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Environmental Factors Altering Thyroid Function and Their Assessment

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Chronic ingestion of modest doses of dietary iodine, radiation, and polyhalogenated biphenyls (PCB's and PBB's) are environmental factors with known or suspected adverse effects on the human thyroid. Iodine consumption in the United States is approaching 1 mg daily for a large segment of the population. Data are reviewed which support the need for concern regarding the long-term adverse effects of dietary iodine on thyroid function, particularly in certain susceptible individuals. Environmental sources of radiation pose a significant risk of thyroid cancer and hypothyroidism under certain circumstances which may be intentional, inadvertent, or accidental. Exposure to polyhalogenated biphenyls during manufacture or as industrial pollutants are hazardous to man and to wildlife in moderate or large quantities and perhaps also in small amounts. The need to investigate the potential harm posed by these factors in the quantities commonly encountered is emphasized.

A wide variety of environmental agents adversely affect the thyroid gland. Some have been precisely identified while others are not well characterized. Some are known to alter thyroid function under unusual circumstances, but are only suspect in the quantities ordinarily encountered. This review will be limited to several agents whose occurrence within the environment is a by-product of technology and whose effects may potentially extend to a large number of people. Initially, the adverse effects of environmental toxins on thyroid function will be discussed with emphasis on their clinical and laboratory evaluation. Subsequent sections of this review will concern the adverse thyroidal effects, proven or suspected, of modestly high dietary iodine consumption, environmental sources of radiation, and polyhalogenated biphenyl exposure.

Assessment of Thyroid Toxicity

Categorically, the major thyroidal abnormalities include hypothyroidism, hyperthyroidism, goiter, and carcinoma. Environmental agents which adversely affect the thyroid assume clinical importance by their ability to induce any one or more of these problems. None are unique to environmental toxins and consequently evaluation of suspected environmental toxin-related thyroid disease proceeds along the same diagnostic routes as does the investigation of spontaneously occurring thyroid disease.

Hypothyroidism is suggested clinically by inexplicable fatigue, cold intolerance, menstrual irregularities, or constipation, among a wide variety of other nonspecific symptoms. A goiter may be present on physical examination. Hyperthyroidism is characterized by nervousness, weight loss, heat intolerance, or palpitations, among other symptoms. A goiter or nodular thyroid is usually present on examination. Smooth or nodular goiters are associated with a variety of thyroid diseases and do not imply concurrent hypofunction or hyperfunction. If present, symptoms are usually attributable to hypo- or hyperthyroidism. Large goiters may pose cosmetic problems or present with symptoms suggestive of tracheal compression. Thyroid cancer is considered in the differential diagnosis of a palpable thyroid nodule; positive diagnosis is made histologically after biopsy or surgical excision. Thyroid cancer patients are generally euthyroid and asymptomatic.

The laboratory evaluation of subjects with suspected thyroid dysfunction, goiter, or potentially malignant nodules is illustrated in Figure 1. Serum thyroxine (T_4), serum triiodothyronine (T_3), free T_4

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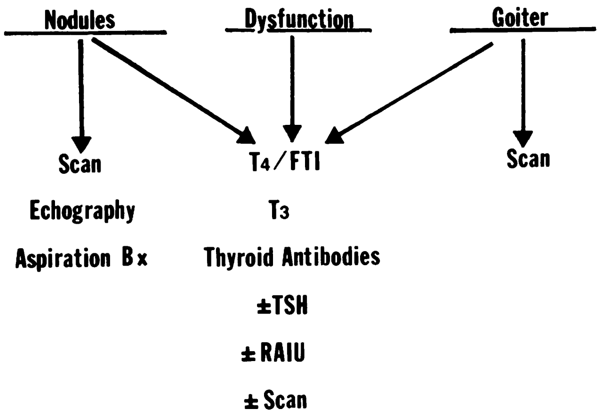

FIGURE 1. Laboratory evaluation of thyroid dysfunction, nodules, or goiter.

or free T_4 index (FTI), and serum antithyroid antibody titers are useful in the evaluation of all patients with suspected thyroid dysfunction, goiter, or thyroid nodules. The T_4, T_3, and FTI may confirm the suspicion of hypothyroidism or hyperthyroidism, or reveal clinically inapparent degrees of hypothyroidism or hyperthyroidism. Primary hypothyroidism, as opposed to the hypothyroidism of pituitary insufficiency, is confirmed by the finding of an elevated serum thyrotropin (TSH) level. The determination of thyroid function in subjects presenting primarily with goiter or thyroid nodules is important because mild hypo- or hyperthyroidism is often not clinically obvious but would nevertheless influence the etiological considerations in subjects with goiters or thyroid nodules. The presence of antithyroid antibodies strongly favors a diagnosis of chronic lymphocytic thyroiditis (Hashimoto's disease) in hypothyroid patients or diffuse toxic goiter (Graves' disease) in hyperthyroid patients. Positive antibody titers in seemingly euthyroid patients with goiters is suggestive of early or very mild Hashimoto's or Graves' disease. Elevated antibody titers in patients presenting with a small thyroid nodule would suggest that the nodule may represent a palpable irregularity of the thyroid commonly found among patients with Hashimoto's disease.

Technetium or ^{123}I thyroid scans are useful in the evaluation of hyperthyroid patients to distinguish diffuse toxic goiter from toxic adenoma or toxic multinodular goiter. These scans are also useful in the evaluation of goitrous patients to help discriminate diffuse goiters from multinodular glands whose structure may be more apparent on the scan than on examination. A thyroid scan is particularly useful in the evaluation of thyroid nodules. Palpable malignant nodules are usually hypofunctional and appear as relatively inactive areas on the scan. Thyroid cysts and benign adenomata may also appear as scintographically hypofunctional areas. With occasional exceptions, functioning nodules are benign. Additional diagnostic information is offered by the degree of thyroid nodularity. A single nodule in an otherwise normal thyroid is more likely to be malignant than a nodule in a uniformly multinodular gland.

Ultrasonagraphy (*1*) is a valuable noninvasive diagnostic technique for distinguishing solid thyroid nodules from simple cysts, the latter being much less likely to be malignant. Needle aspiration biopsy (*2*) yields much the same information plus additional cytological data concerning the malignant potential of the cells.

A radioactive iodine uptake (RAIU) determination is often useful in the evaluation of hyperthyroidism. Factitious hyperthyroidism (self-induced by excessive thyroid hormone ingestion) and "silent" or "painless" thyrotoxicosis (*3-5*) are accompanied by a very low RAIU, whereas the more common forms of hyperthyroidism are associated with normal or elevated RAIU's.

The primary discriminants of toxin-related thyroid disease are historical and epidemiological. On an individual basis the onset of detectable thyroid abnormalities must be carefully considered with respect to the earliest exposure to the suspected toxin. Similarly, the amelioration of symptoms should be considered in terms of the time after cessation of exposure. On a statistical basis the type and prevalence of the suspected thyroidal abnormality within an exposed population should be compared to these same parameters in a comparable but unexposed population.

A family history of thyroid disease should always be obtained from individuals suspected of environment-related thyroid disease. Dyshormonogenetic goiters and autoimmune thyroid diseases exhibit significant hereditary predispositions. Their recognition may suggest that the suspected thyroid abnormality pre-existed the toxic exposure and was induced to become clinically apparent. Certain individuals may be essentially free of disease prior to exposure but are more susceptible to developing thyroidal abnormalities in response to toxic insults than ordinary individuals.

Chronic Ingestion of Modest Doses of Dietary Iodine

Prior to dietary iodine prophylaxis, goiter, hypothyroidism, and cretinism from iodine deficiency had been endemic in many areas of the world. In many areas these problems still exist (*6*). In the United States, goiter had been particularly prevalent along the northern border of the country and in the upper midwestern states. Since the introduction of iodized salt in these areas in the 1920's (*7*), the prevalence of goiter has been dramatically reduced (*8*). By 1970, daily iodine consumption in the U.S. ranged from 238 μg to 738 μg (*9*), as calculated from its effects on the normal ranges of radioiodine uptakes at various centers around the country. Daily iodine consumption in endemic iodine-deficiency areas estimated by direct assay of iodine in 24-hr urine specimens is usually less than 50 μg. The U.S. Recommended Dietary Allowance (RDA) for iodine has most recently been set at 150 μg daily for adults plus an additional 25 μg and 50 μg for pregnant and lactating women, respectively (*10*). Consistent with these determinations, iodine-deficiency in this country is no longer a public health problem.

To the contrary, more recent estimates of daily iodine consumption in the U.S. and Canada indicate that iodine consumption is clearly above the RDA and for most people substantially above the RDA (Table 1). A study of children aged 9-16 in Michigan, Kentucky, Texas, and Georgia in 1971-72 revealed an average iodine intake of 459 μg per day (*11*). An extensive study in 1968-70 covering 36,000 people in ten states revealed that 9.5-21.9% of the people tested excreted in excess of 799 μg iodine per gram of urinary creatinine per day in 7 of the 10 states (*12*). As approximately one-half of the studied population in the seven states were adults [estimated to excrete approximately 1.2 g (females) to 1.5 g (males) creatinine per day], it can be grossly estimated that 5-10% of the test population, or 10-20% of the adults, consumed over 1 mg of iodine per day. A 1970-72 nutritional survey of Canada revealed that approximately 5% of the adult population consumed 500-700 μg iodine/g urinary creatinine, or in the order of approximately 0.8 mg iodine per day. Perhaps 2% of the population consumed in excess of 850 μg iodine/g creatinine, or in excess of 1 mg of iodine per day (*13*). Over 15 years ago, healthy individuals near Washington, D.C. were calculated to consume over 0.8 mg of iodine daily, ranging up to 1.5 mg per day, on 20% of days studied (*14*). Analysis of the adult Market Basket Surveys of 1974 and 1975 indicate an average daily iodine intake of 784 μg and 642 μg, respectively, in those consuming a 2800 calorie diet (*15*). Addition of 260 μg of iodine from 3.4 g of iodized table salt (*16*) brings the average daily iodine intakes to approximately 1 mg per day. As a result of the studies involving direct measurement of plasma or urinary iodide and the observations of progressively declining normal ranges for radioactive iodine uptakes (*17-19*), the trend toward increased iodine consumption in the U.S. has not gone unrecognized (*15, 20-23*).

Although it is very difficult to project an estimated average daily iodine consumption for children and for adults in the U.S. in 1980, it is probably fair to assume that at least 10% of the adult population, and possible much more, consume in excess of 1 mg iodine per day and that a comparable percentage of children may be consuming an iodine load proportionate by body weight to the adult consumption. Since it can be calculated that approximately 260 μg of iodine are consumed daily in table salt iodized at the 1:10,000 level (100 μg KI/g salt or 75 μg iodide/g salt), it becomes apparent that most ingested iodine is obtained from less obvious dietary sources (*16*). Ingestable iodine is commonly found in a wide variety of foodstuffs, food coloring and seasonings, food processing agents, and medicaments. The bulk of dietary iodine, however, is probably derived from milk and other dairy products and from bread prepared with iodate as a dough conditioner (*15*). The many and diverse uses for iodine in the food and dairy industry give reason to suspect that dietary sources of iodine are not likely to decline until an equally diverse group of alternative agents are identified and implemented.

At present it is impossible to be certain that chronic ingestion of modest amounts of iodine would have adverse effects on thyroid function although there is considerable evidence that supports the wisdom for concern. If even a few percent of the population ingest in excess of 1 mg of iodine

Table 1. Estimates of high iodine intakes among adults.

Study	Source	Year	Estimate
Washington, D.C. Suburbs	Vought and London (*14*) Vought (*20*)	1964	> 0.8 mg on 20% of days sampled
Ten-State Nutritional Survey	Trowbridge et al. (*12*)	1968–70	⩾ 1 mg in 10–20%[a]
Saskatchewan Survey	Nutrition Canada (*13*)	1970–72	⩾ 0.8 mg in 5%
Market Basket Survey	Harland et al. (*15*).	1974	1 mg (average)[b]
Market Basket Survey	Harland et al. (*15*)	1975	0.9 mg (average)[b]

[a] In seven of the ten states, assuming that the finding of urinary iodine excretion > 799 μg/g creatinine per day was equally common in adults and children.

[b] For adults consuming a 2800 kcal diet including 3.4 g of iodized salt daily.

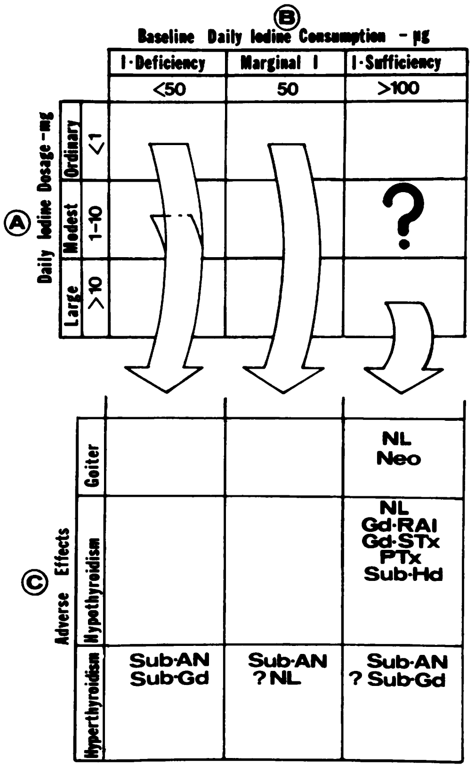

FIGURE 2. Adverse effects of iodine reported in susceptible individuals. Iodine in varying dosages (*A*) has been introduced into societies accommodated to different levels of daily iodine consumption (*B*) resulting in adverse effects (*C*) in normal individuals (NL); neonates (Neo); patients with subclinical autonomously-functioning nodules (Sub-AN), Graves' disease (Sub-Gd) or Hashimoto's disease (Sub-Hd); patients with Graves' disease previously treated with radioactive iodine (Gd-RAI) or by subtotal thyroidectomy (Gd-STx); and patients previously treated for benign thyroid nodules by partial thyroidectomy (PTx).

daily, substantial numbers of people are involved. Certain potentially susceptible groups of people, e.g., the unborn and those with subclinical thyroid disease, may face a slight but unrecognized risk from quantities of iodine too little to affect ordinary individuals. As depicted in Figure 2, interpretation of the large body of data relevant to the adverse effects of iodine on thyroid function requires appreciation of the baseline daily iodine ingestion of the subject population, the daily quantity of iodine to which the subject population is being introduced, the rate of introduction of increased levels of iodine into the population, the presence and nature of any underlying susceptibilities to overt thyroid dysfunction, and the type of thyroid abnormalities reported to result from the exposure.

There are numerous reports of iodine-induced hyperthyroidism (Jod-Basedow phenomenon) when iodine, sometimes in quantities less than 1 mg daily (*24*), were introduced into iodine-deficient populations (*25, 26*). Subsequent study (*27*) support the theory that the induced hyperthyroidism is a manifestation of underlying autonomously-functioning thyroid nodules or Graves' disease. Assumedly, the underlying disease had been silent only for lack of available substrate for thyroid hormone production. Administration of ordinary amounts of iodine (several hundred µg per day) to subjects in areas of minimally adequate quantities of dietary iodine, e.g., parts of western Europe, has been reported to induce hyperthyroidism in subjects with nodular thyroids (*28*) and in some individuals without apparent underlying thyroid disease (*29*). It does not follow, however, that this phenomenon would be reproduced by superimposing comparably small amounts of iodine on a population which has been chronically exposed to more than adequate sources of iodine.

There are reports of thyroid dysfunction arising in subjects living in iodine-sufficient areas (greater than 100 µg iodine per day). With very few exceptions the reported cases involve administration of pharmacological doses of iodine, here regarded as greater than 10 mg per day but generally in excess of 100 mg per day. Ingestion of large quantities of iodine by pregnant women is well known to induce goiter (*30, 31*) and less commonly hypothyroidism (*31, 32*) in the fetus. At times these goiters have resulted in tracheal compression and neonatal asphyxiation. Normal individuals are also at a small but definite risk of developing goiter and occasionally hypothyroidism during chronic ingestion of pharmacological doses of iodine (*30, 33, 34*). Perhaps most well known are the residents of coastal areas of Hokkaido, Japan who consume 8-200 mg of iodine per day (*35*). School children of these areas maintain a 25% prevalence of goiter. Patients with chronic obstructive pulmonary disease (*36*) or cystic fibrosis (*37*) treated with 450 mg of iodine or more per day have been reported to develop goiter, often associated with hypothyroidism.

Hypothyroidism has also been described as a primary consequence of the administration of large doses of iodine to euthyroid individuals in iodine-sufficient areas. Four of seven euthyroid patients with underlying Hashimoto's thyroiditis became hypothyroid within 4-6 weeks of treatment with 180 mg of iodine per day (*38*). Patients with hyperplastic or regenerating thyroid tissue as seen after partial thyroidectomy for thyroid nodules (*39*) or Graves' disease (*33, 38*) or after radioactive iodine therapy of Graves' disease (*33, 40, 41*) have also been shown to become hypothyroid after the administration of large doses of iodine.

The induction of hyperthyroidism in iodine-sufficient individuals by large doses of iodine has also been reported. Patients with euthyroid nodular goiters have been shown to become hyperthyroid after several weeks of treatment with 180 mg iodine per day (*42*). An asthmatic child with a family history of goiter and hyperthyroidism, treated with well over 1000 mg of iodine per day, was observed to become thyrotoxic within four months of initiation of treatment and improved promptly after discontinuation of the medication (*43*). Iodine derived from radiographic contrast media has also been reported to induce hyperthyroidism in a patient with a nontoxic, autonomous thyroid nodule (*44*). But the potential for pharmacological doses of iodine to induce goiter, hypothyroidism or hyperthyroidism in iodine-sufficient healthy individuals, or even in susceptible individuals, may not necessarily be applicable to modest doses of iodine in the 1-10 mg per day dosage.

It should be noted that relatively small doses of 0.5 mg iodine are capable of inducing abnormal perchlorate discharge tests in some euthyroid patients with mild Hashimoto's disease (*38, 45*) and that this characteristic may identify which of these patients are prone to become hypothyroid after treatment with large doses of iodine (*38*). The same phenomenon has been observed in euthyroid patients previously treated with radioactive iodine for Graves' disease (*33*). It does not follow, however, that chronic exposure of patients with subclinical disease to a diet incremented by 0.5 mg of iodine per day would necessarily lead to clinically apparent disease. Interestingly, this dose of iodine has been alleged to induce hyperthyroidism in one patient within several weeks (*46*).

The effects on thyroid function of chronic iodine consumption in the 1-10 mg per day range have not been adequately investigated. A most informative study concerning this topic involves a prison population whose source of drinking water contained 0.5 mg/l. of iodine as a disinfectant (*47, 48*). Daily iodine consumption was probably in the order of 1-2 mg daily for up to 3 years. Not surprisingly, their 24-hr radioactive iodine uptakes dropped from an average of 17% to 7.2% without change in the serum thyroxine levels. No cases of goiter or hypothyroidism were thought to result from this exposure, although four inmates who may have had mild symptoms of hyperthyroidism when entering prison became frankly thyrotoxic during their imprisonment. Two patients exhibited elevations in their serum thyroxine levels after discontinuing the water, but normalized their thyroxine levels when again exposed the water. Importantly, no neonatal goiters or increased incidence of congenital anomalies were observed in 181 full-term neonates of imprisoned mothers.

The findings of several studies suggest that increases in iodine consumption may favor induction of Hashimoto's thyroiditis. The prevalence of histologic thyroiditis in thyroidectomy specimens appears to have increased after the introduction of iodine prophylaxis in the United States (*49-51*). Lymphocytic thyroiditis was rarely found in thyroid specimens of untreated patients with iodine-deficiency goiters in the Himalayas (*52*). Administration of large amounts of iodine to rats and hamsters has been reported to induce lymphocytic infiltration of the thyroid (*53, 54*). Addition of iodine to immunogenic preparations of thyroid extracts has also been shown to induce a histologically more humanlike lymphocytic thyroiditis in beagles (*55*). However, the animal models may not be equivalent to the human disease. The prevalence of physical and laboratory features of Hashimoto's thyroiditis and Graves' disease in contemporary school children (*11, 56, 57*) is surprisingly high but not of itself indicative of a causative or exacerbating role for iodine. These and other studies have been previously considered with the general impression that the evidence for a role of iodine in the pathogenesis of chronic lymphocytic thyroiditis remains inconclusive (*23*).

The induction by iodine of goiter or abnormal ^{131}I uptake and perchlorate discharge tests in patients with Hashimoto's thyroiditis rather argue that these patients are particularly susceptible to the adverse effects of iodine, perhaps less capable of escaping the Wolff-Chaikoff block (*58*). It has been suggested that iodides enhance a pre-existing intrathyroidal organification defect in patients with Hashimoto's thyroiditis (*59*).

Other adverse effects of modest iodine ingestion have been suggested. The increasing consumption of iodine over the 10-year period from 1962 to 1972 has been hypothesized to effect a reduction in the remission rate of antithyroid drug therapy of Graves' disease (*60*). Administration of iodine to patients withdrawn from antithyroid drugs has had somewhat conflicting effects on remission rates (*61, 62*). The relatively high incidence of papillary thyroid cancer in Iceland and Japan, two countries with relatively high daily iodine consumption, has been pointed out (*63, 64*), but the putative association of thyroid cancer and increased iodine consumption is open to other interpretations (*23*). Acne, ioderma, and a wide variety of adverse effects not related to the thyroid have been thoroughly reviewed elsewhere (*65*).

At present the evidence that chronic iodine intake in the order of 1-10 mg daily presents a significant risk of thyroid dysfunction is largely circumstantial but, in view of the size of the potential target population, the trend toward increased iodine consumption, and the more probable success of earlier rather than later intervention, the question merits serious evaluation. This issue has, in fact, been the topic of a recent workshop (*66*). Recommendations forthcoming from this workshop are anticipated to include an appeal to limit further increases in dietary iodine input until the biological safety of chronic, modest iodine ingestion is more firmly established.

Environmental Sources of Radiation

There is little doubt that under appropriate circumstances radiation exposure can induce a variety of thyroid-related abnormalities. Treatment of hyperthyroid patients with ^{131}I has been observed to exacerbate the hyperthyroidism (*67, 68*), presumably by releasing stored hormone from radiation-damaged tissue. There are numerous reports of primary hypothyroidism arising after radiation exposure to the thyroid (*69, 70*). High radiation doses (> 1,000 rem) to the thyroid administered as ^{131}I for the treatment of Graves' disease (*40*) and cardiac disease (*71, 72*), or as external radiation to the head and neck for regional carcinoma (*69, 70, 73*) are known to induce hypothyroidism particularly at very high dosages (> 25,000 rem). Exposure to external radiation less than several hundred rem appears to involve very little risk of hypothyroidism (*74-76*), although a threshold as low as 20 rem has been suggested (*69*) for ^{131}I exposure.

Induction of thyroid cancer by radiation has been considered under a wide variety of circumstances. As outlined in Table 2, radiation exposure can be intentional, inadvertent, or accidental. Intentional destruction of thyroid tissue with administration of ^{131}I is a common and effective therapy for Graves' disease and was formerly used for the amelioration of angina pectoris (*71*). In smaller doses ^{131}I and ^{123}I are often used in diagnostic thyroid scans and uptake measurements. Typical thyroidal radiation exposures from these procedures are given in Table 3. Thyroid exposure to radiation also occurs inadvertently. Significant thyroid exposure to radiation results from radiotherapy for lymphomas and other carcinomas of the head and neck, and from the now discontinued use of radiation for tonsillar or thymic enlargement, acne, pertussis, and tinea capitis among other benign illnesses (*77*). Inadvertent exposure from both external radiation and from inhaled or ingested ^{131}I has been studied in those exposed to nuclear weapon testing (*75, 78-80*) and to the survivors of the Hiroshima and Nagasaki blasts (*81, 82*). Accidental exposure to the radioisotopes of iodine has long been a risk to laboratory workers and technicians and, as recently drawn to wide public attention (*83*), may pose a risk to many after nuclear reactor accidents.

Table 2. Sources of thyroidal radiation exposure.

Type	Source
Intentional	Treatment of Graves' disease with ^{131}I
	Treatment of angina pectoris with ^{131}I
	Diagnostic thyroid scanning with ^{131}I or ^{123}I
Inadvertent	Radiotherapy of head and neck cancer
	Radiotherapy of benign diseases
	Atom-bomb blasts (Hiroshima and Nagasaki)
	^{131}I-Fallout from nuclear weapons testing
Accidental	Laboratory accidents
	Nuclear reactor accidents

Table 3. Approximate thyroidal radiation exposure from isotopes of iodine.

Procedure	Dose	Exposure (rads)[a]
^{131}I treatment of angina	30 mCi	30,000
^{131}I treatment of Graves' disease	5mCi	5,000
^{131}I scan	50μCi	50
^{131}I uptake	6 μCi	6
^{123}I scan	300 μCi	2
^{123}I uptake	50 μCi	0.4
^{99m}Tc scan	3000μCi	1

[a]Rads are equivalent to rems for radioisotopes of iodine.

Radiation exposure to the thyroid in excess of approximately 25,000 rem involve a significant risk of inducing hypothyroidism but seems to involve minimal risk of carcinogenesis when employed for the relief of cardiac disease (*69, 84, 85*). Expectedly, lethal doses of radiation would greatly reduce the population of cells available for carcinogenesis. The lesser degree of radiation exposure to the thyroid involved in the treatment of Graves' disease with ^{131}I, generally 5,000-10,000 rem, similarly does not appear to involve a significant risk of carcinoma. A number of studies (*86-89*) indicate that carcinogenesis is not a significant risk at doses in excess of approximately 2000 rem, and that ^{131}I therapy for Graves' disease does not impose a risk of carcinogenesis (*85, 90, 91*).

Radiation exposure from diagnostic ^{131}I thyroid scans is considerably less than therapeutic exposure but is perhaps not insignificant. A 50 μCi ^{131}I scan would deliver an approximate exposure of 80 rem to an adult thyroid and two or three times that to a child's thyroid (*92*). The studies of Rallison and others (*75, 79*) on the schoolchildren exposed to comparable amounts of radiation from nuclear testing suggests that 50-100 rem may approximate the threshold below which there is no appreciable risk of carcinogenesis. One case of thyroid carcinoma following diagnostic studies has been reported (*93*). Available information suggests that ^{131}I scans approach the exposure level thought to pose a probable though small risk of carcinogenesis.

Radiation therapy of lymphomatous cervical lymph nodes or other carcinomas of the head and neck may involve considerable exposure to the thyroid, often enough to result in primary hypothyroidism (*70*). Anecdotal cases of thyroid cancer in patients previously subjected to radiotherapy of head or neck carcinoma have been noted in several reports and letters (*94-99*) as well as in the author's own experience. Likely, the generally higher radiation exposure and older age of those subjected to radiotherapy of head or neck malignancy account for the lower incidence of thyroid cancer in these patients.

In the 1940's and 1950's low-dose radiotherapy was commonly used for a variety of benign problems of infancy and childhood (*77*). Depending on the dose of applied radiation and the proximity of its field to the anterior neck, thyroid exposure could range from virtually nil to over a thousand rem. It was subsequently observed that children with thyroid cancer had a frequent history of prior radiation for benign problems (*100-102*). Since then, numerous reports have confirmed the association of low-dose radiation exposure and thyroid cancer (*76, 103-106*). Analysis of several studies demonstrate a dose-dependent risk of post-radiation carcinogenesis up to approximately 1000-1500 rem (*69, 86, 107*). It is unclear if radiation exposures below 20 rem are associated with a risk of carcinoma (*74*). The latent period for detection of thyroid carcinomas after radiation exposure is generally ten or more years and may extend up to or beyond 40 years (*76, 86, 97, 108-110*).

Radiation exposure from nuclear weapons includes both direct, external radiation and exposure from absorbed or ingested radioisotopes of iodine (particularly ^{131}I) derived from the fallout. Survivors of the Hiroshima and Nagasaki A-bomb blasts studied 13-16 years after exposure were not found to exhibit a greater prevalence of thyroid cancer when compared to a contemporary non-exposed clinic population, although the prevalence of thyroid cancer among the exposed patients appeared to be inversely proportional to their distance from the hypocenter of the blast (*82*). In a subsequent study (*81*) of the A-bomb survivors 13-26 years after the blasts, the prevalence of thyroid cancer was indeed found to be higher in all those exposed to 50 or more rads of radiation, particularly if the individuals were less than 20 years of age at the time of exposure.

Of 67 Marshall Islanders inadvertently exposed to direct gamma-radiation and to ^{131}I, ^{132}I, ^{133}I, and ^{135}I fallout, 21 developed thyroid abnormalities including three malignancies, 16 benign nodules, and two cases of hypothyroidism (*78*). The adult exposure on the first day was in the order of 160 rads from ^{131}I and 175 rads from gamma-radiation. Children under age 10 seemed to have a much higher propensity to develop a thyroid abnormality, possibly as a result of their generally threefold higher radioiodine exposure. It may also be true that thyroid tissue in children is more susceptible to radiation damage than adult tissue (*111*).

Infants and children aged 8 or less at the time of exposure to the fallout in southwestern Utah following the Nevada nuclear weapons tests in the early 1950's were found to have no greater prevalence of thyroid nodularity than a control, nonexposed population (*79*). The target population was studied approximately 10 years after an estimated thyroid exposure of 5-50 rads and perhaps more than 100 rads in some cases. Radiation exposure from the Nevada tests was thought to be largely acquired from ^{131}I-contaminated milk. Minute doses of radioactivity have also been detected in fetal human thyroids after maternal exposure to ^{131}I-containing fallout from the nuclear weapons testing in 1958 by the United States, Great Britain, and the Soviet Union (*112*).

Accidental ingestion of ^{131}I or ^{125}I has occurred in laboratory technicians during radio-iodination procedures for labeling proteins. Ingested doses could range from the trivial to several millicuries. The latter situation would to some extent mimic the treatment of Graves' disease although iodine turnover and tissue sensitivity to radioiodine would be lower in normal thyroid glands. In a study comparing the efficacy of ^{125}I treatment of Graves' disease to that of ^{131}I, the former isotope resulted in a greater degree of hypothyroidism (*113*).

Nuclear reactor accidents have the potential of exposing many people to significant amounts of thyroid radiation exposure. Huge amounts of volatile and water-soluble radioisotopes of iodine can be generated, of which ^{131}I and ^{133}I are the most important (*114*). Fortunately, in the recent mishap at the Three Mile Island Nuclear Station in March, 1979, the preponderance of radioiodine isotopes was well contained. In a preliminary study (*83*) in which milk samples in the immediate area were assayed for ^{131}I, only one-fourth of the samples contained the isotope in concentrations ranging from 1-41 pCi/l. It was calculated that an infant drinking 1 liter of the most heavily contaminated milk would be subjected to 5 mrem of thyroidal radiation; an adult consuming the same quantity would be subjected to only one-tenth that amount.

These exposures are well below the estimated annual total body radiation exposure from unavoidable sources of cosmic and terrestrial radiation. Estimated ^{131}I intake from the air was similarly miniscule.

Radiation-associated hyperthyroidism, hypothyroidism, and carcinogenesis are not clinically distinct from the spontaneously occurring thyroid diseases. Except perhaps for the histological features of radiation-fibrosis or radiation-thyroiditis, the etiology of the radiation-associated thyroid abnormalities become apparent only by uncovering the historical and epidemiological features of radiation exposure in affected individuals.

Polyhalogenated Biphenyls

Polyhalogenated biphenyls are commonly used compounds with a wide variety of industrial applications. Polybrominated biphenyls (PBB's) have been used as flame retardants. Polychlorinated biphenyls (PCB's) are used as lubricants, adhesives, inks, hydraulic fluids, and as plasticizers (*115*). The environmental impact of the PCB's derives from their presence as pollutants in lakes and rivers and their capacity to accumulate in the adipose tissue of fish and fish-eating predators, including man (*115*). There is little question that the PCB's affect the thyroid function of animals. Extensive (*116-118*) and brief reviews (*119*) of the social and biological impact of the PCB's are already available, and so this review will focus primarily on the studies pertinent to the potential adverse effects on human thyroid function.

The preponderance of animal data implicate the PCB's as inducers of goiter and hypothyroidism. Coho salmon from the Great Lakes have exhibited a high prevalence of goiter in recent years (*120-122*). The very low iodine content of the Great Lakes compared to sea water (*123*) is probably partially responsible for the goiters in these fish. It has been demonstrated decades ago that rainbow lake trout were more commonly goitrous than those found off California (*124*). Recent analysis reveals that the frequency of Coho salmon goiter is not inversely proportional to the iodine content of the lakes from which the Coho were obtained (*122*). Further, the incidence of goiter among the Coho population appears to be increasing in recent years, whereas the iodine content of the water is essentially stable. These observations are consistent with the interpretation that the increasing incidence of goiter reflects increasing lake pollution (not necessarily limited to PCB's). It has also been shown that PCB's are capable of inducing thyroid abnormalities when fed to Coho (*123*). As consumers of other fish, and perhaps being less well adapted to a low iodine environment than fish indigenous to the Great Lakes, the Coho are more likely to accumulate fat-soluble goitrogens and may be more susceptible to goitrogenesis. In addition to goiter, the Coho have exhibited markedly depressed thyroxine and triiodothyronine levels (*121*). Histological features suggestive of thyroid cancer have also been reported (*120*).

The molecular mechanisms of PCB-induced goitrogenesis and hypothyroidism have been systematically studied in rats cutaneously exposed to PCB-containing immersion oil (*125*). Compared to unexposed controls, the PCB-exposed animals exhibited decreased serum thyroxine (T_4) but not triiodothyronine (T_3) levels. It appeared that PCB displaced T_4 from the serum proteins, accounting for the low total T_4 levels. Additionally, increased biliary excretion and loss of T_4, possibly related to the induction of T_4-UDP-glucuronyl transferase, may have contributed to the simultaneously reduced free T_4 index. Enhancement of peripheral T_4 to T_3 conversion was thought to explain the absence of simultaneous reductions in the serum T_3 level and free T_3 index. Thyroid enlargement has also been observed in rats treated with PCB's (*126*) or PBB's (*127*).

After long-term contact with PCB in more than trace quantities, humans may develop an acnelike skin rash, weakness, headaches, gastrointestinal disturbances, irritation of the eyes, nose and throat, swollen extremities, and many other symptoms (*128*, *129*). In 1968, over 1000 people in southwestern Japan were afflicted with a syndrome, usually beginning with a chloracnelike skin eruption now known as Yusho disease. The epidemic was traced to PCB-contaminated rice oil used for cooking (*129*). Subsequently, 22 deaths were associated with the PCB exposure, including nine malignancies of various types (*128*). No specific thyroid abnormalities were reported.

PCB is present at 5 mg/kg in lake fish (*115*) and is also found in the adipose tissue of a surprising 30-45% of the general public (*130*, *131*). It is uncertain, however, if there are any adverse health effects pursuant to this order of exposure. Hematology technicians working with PCB-containing microscope immersion oil exhibited no abnormalities when screened for decreased serum T_4 levels and increased thyrotropin levels as indicators of early hypothyroidism (*125*). A recent evaluation of 35 workers in a PBB manufacturing plant (*132*) identified four cases of primary hypothyroidism, whereas no cases were found among 89 control subjects. These same four cases had markedly elevated titers of antithyroid microsomal antibodies suggesting that the hypothyroidism was a manifestation of chronic lymphocytic thyroiditis, perhaps a PBB-induced exacerbation of pre-existing but subclinical disease. There was not statistically significant difference in the prevalence of elevated antimicrosomal antibody titers between the control and exposed groups. PBB's also have been reported to cause decreased serum T_4 levels in rats (*127*).

In a subsequent report, 51 subjects were evaluated who had been exposed to PBB's and found to have abnormal serum or adipose levels of this compound (*133*). Neither thyroid nodularity or goiter, nor unusual incidence of abnormal serum T_4, thyrotropin or T_3-resin uptake were found. As suggested, the absence of abnormalities must be viewed with the understanding that PBB's may have a long latent period and falsely appear innocuous. The evidence for harm by PCB and PBB exposure in the quantities commonly encountered by the average person is still inconclusive.

In parallel to the potential hazards perceived for the chronic ingestion of modest amounts of iodine, individuals with greater than average exposure and those with a greater susceptibility to the compounds are likely to be the first to manifest goiter or hypothyroidism.

Conclusion

The recurrent theme in the consideration of iodine, radiation, or polyhalogenated biphenyls as environmental thyroid toxins in the quantities commonly encountered is that there appears to be abundant evidence for suspicion but scant evidence for definitive conclusions. In part this may reflect our intrinsically more rapid capacity to apply technology than to evaluate it, but also reflects the lag phases from the introduction of an agent into the environment to the uncovering of specific and relevant questions concerning its impact, and from the recognition of relevant questions to the determination of the answers. With each of these agents it is hoped that the important questions concerning their thyroid toxicity have been recognized and that the answers will be adequately pursued.

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